rejections and objections have been traversed, and therefore allowance of these claims is earnestly solicited.

Prior to responding to the Office Action, a brief summary of the present invention may advance the prosecution of this case to issuance. The present invention relates to methods of effectively inactivating pathogens in biological materials without degrading or inactivating associated proteins. Accordingly, claims 43, 62, 65, 66, 71, and 72 have been amended to better clarify the methods of the present invention.

Rejections under 35 USC §112

Claims 65-66, 71, and 72 are rejected under 35 USC §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

In response, claims 65, 66, 71, and 72 have been amended according to the Examiner's suggestions. Applicants respectfully submit that the rejections to claims 65-66, 71, and 72 have been traversed, and the claims, as amended, are definite under 35 USC §112, second paragraph.

Rejections under 35 USC §102(e)

Claims 43-48, 50-55, 57-60, 62-64, and 73-75 are rejected under 35 USC §102(e) as being anticipated by Evans et al. (U.S. Patent No. 5,989,421). It appears that the Examiner has inadvertently cited an incorrect Patent number, and the Applicant assumes that the Examiner meant to reference U.S. Patent No. 5,989,431.

The Examiner states that the present invention is anticipated by Evans because while "Evans does not expressly teach a method for inactivating microorganisms and pyrogens present in biological materials, however, the process steps, the ingredients used, the materials to be treated, and the experimental parameters and conditions taught by Evans are the same or essentially the same as disclosed in the claimed

invention. Thus, the result would be the same or essentially the same result as disclosed in the instant invention." (2/8/01 Office Action, pg. 5).

The Applicants respectfully submit that the present invention is not anticipated by Evans. The distinction between the Evan's processes and the methods of the present invention is further illustrated when the preambles are compared. Evans is directed to DNA extraction whereas the present invention teaches pyrogen and microorganism inactivation. In other words, Evans and the present invention are directed to two distinct methods. Moreover, as previously asserted the present invention is directed to inactivating microorganisms and pyrogens while maintaining protein integrity. In contrast, Evans does not disclose any methods of stabilizing proteins while pathogens are inactivated by eluotropic salts. Rather, Evans is directed to methods of extracting DNA from cell suspensions. Evans is not concerned with the other components in the cell suspension or pyrogen/microorganism inactivation but rather efficient extraction of DNA. Nowhere does Evans teach pyrogen or microorganism inactivation while maintaining protein integrity. Because Evans does not teach the stabilization of proteins during the pathogen inactivation, Applicants respectfully submit that the rejections to claims 43-48, 50-55, 57-60, 62-64, and 73-75 have been traversed and are allowable.

Rejections under 35 USC §103(a)

Claim 56 is rejected under 35 USC §103(a) as being unpatentable over Evans in view of Commission of the European Communities, "Ad Hoc Working Party on Biotechnology/Pharmacy Guidelines" (hereinafter "Guidelines"). Specifically, the Examiner states that "Evans does not teach a method wherein the step of incubation is performed in the prescribed periods of time between 1 hour and 5 hours. However, it would have been obvious to one of ordinary skill at the time the invention was made to modify the incubation times to provide a method for inactivating microorganisms and pyrogens wherein the microorganisms are viruses because Evans expressly teaches that the incubation procedure for the lysis of the cells can be repeated several times."

To make up for the deficiency of Evans, the Examiner cites the Guidelines as teaching criteria necessary for designing methods for testing the efficacy of a viral inactivation procedure or purification methods for the production of biological materials.

Applicants respectfully submit that the present invention is not obvious in light of Evans and the Guidelines. As previously asserted, the present invention is directed to providing methods that permit pathogen inactivation while stabilizing proteins on a solid resin or chromatographic support. In contrast, Evans does not teach or disclose any methods of stabilizing proteins on a solid carrier. Moreover, Evans uses 4M guanidine thiocyanate which is known to readily dissolve proteins. Evans does not teach or suggest the problem that the present invention solves, namely an effective method of inactivating pathogens while maintaining protein integrity. Thus, it is respectfully submitted that the rejection have been traversed, and the present invention is not obvious in light of Evans and the Guidelines.

Claims 46, 61, and 65-70 are rejected under 35 USC §103(a) as being unpatentable over Michalski in view of Evans, and further in view of admitted prior art. The Examiner states that "Michalski teaches a process for the viral inactivation and purification of the PPSB fraction of human plasma in the preparation of a human thrombin concentrate." To make up for the deficiency of Michalski, the Examiner states that "it would have been obvious to one of ordinary skill in the art to modify the teachings of Michalski by replacing the step of inactivation taught by Michalski because Evans teaches a method for lysing a suspension of cells in the presence of a lysis solution." The Examiner concludes that "one of ordinary skill in the art would have been motivated and one would have a reasonable expectation of success to substitute the method of viral inactivation taught by Michalski for the viral inactivation taught by Evans because Evans' lytic solution is effective in the lysis of cells contained in a body fluid such as blood, and it is well known in the art that the lysis of cells renders the cells inactive or kills the cells.

It is respectfully submitted that the present invention is not obvious over Michalski in view of Evans. Applicants respectfully submit that the present invention is not obvious because the combination of the prior art references do not teach or suggest all the requirements of the claimed invention. This is evidenced by the fact that the cited prior art references, do not contemplate a solution to the problem of protein degradation. Specifically, the Michalski and Evans references do not teach the adsorption of the biological components onto a solid carrier. The solid carrier of the present invention allows for the stabilization of proteins and other biological components while concomitantly exposing pathogens to inactivating agents. Because Michalski and Evans do not teach or suggest the stabilization of protein structure during pathogen inactivation, it is respectfully submitted that the rejections to claims 46, 61, and 65-70 have been traversed and allowance of the claims is earnestly solicited.

Furthermore, there is no reasonable expectation of success given the teachings of Michalski and Evans. That is, given the teachings of Michalski and Evans, one of ordinary skill in the art would not be able to enable the methods of the present invention. As previously asserted, Evans uses known protein degrading agents such as 4M guanidine thiocyanate to lyse cells to maximize DNA extraction. The use of protein denaturants is contrary to the goal of the present invention of stabilizing and maintaining protein structure during pathogen activation. Because the Michalski and Evans reference fail to teach or suggest the step of adsorbing proteins onto a solid carrier, and a person of ordinary skill in the art would not have a reasonable expectation of success, it is respectfully submitted that claims 46, 61, and 65-70 are not obvious under 35 USC §103(a) and are allowable.

Claim 71 is rejected under 35 USC §103(a) as being unpatentable over Michalski in view of Evans, and in further view of Isakkson, and further in view of Eibl. The Examiner states that it would have been obvious to modify the combined teachings of Michalski and Evans by adding heparin to the eluting solution because Isakkson teaches a process for the inactivation of virus in blood products by adding heparin to an

elution solution in the production of a prothrombin complex product, in order to prevent an activation of prothrombin, as evidenced by the teachings of Eibl. The Examiner concludes that "the claimed invention is no more than the additive effect of well known ingredients and method steps in the making of well known products."

The Applicant respectfully submits that the Examiner has impermissibly used hindsight to render the present invention obvious. Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability—the essence of hindsight. *In re Dembiczak*, 175 F.3d 994, 999 (CAFC 1999). The *In re Dembiczak* court further states:

> "evidence of a suggestion, teaching, or motivation to combine may flow from the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem solved, although 'the suggestion more often comes from the teachings of the pertinent references,' In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998). The range of sources available, however, does not diminish the requirement for actual evidence. *That is, the showing must be clear and particular.* See, e.g., C.R. Bard, 157 F.3d 1340, 1352, 48 USPQ2d. 1225, 1232 (Fed. Cir. 1998). *Broad conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence'*" (emphasis added). *In re Dembiczak,* 175 F.3d at 999.

As previously asserted, the Examiner states that "the claimed invention is no more than the additive effect of well known ingredients and method steps in the making of well known products." The Examiner has not provided any actual evidence in the Michalski, Evans, Isakkson, or Eibl references that demonstrate a teaching or motivation to

combine the reference. Nowhere in these references is there any disclosure of relating to the stabilization of proteins during pathogen inactivation. Furthermore, it is respectfully submitted that the prior art references did not contemplate the problem the present invention solves, namely, inactivating pathogens while maintaining protein structure. Thus, it is respectfully submitted that the rejection to claim 71 has been traversed and allowance of the claim 71 is respectfully requested.

Conclusion

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned **"Version with markings to show changes made"**

Applicants respectfully submit that all the objections and rejections to the claims of the present invention have been traversed. Therefore, all claims presently on file in the subject application are in condition for immediate allowance, and such action is respectfully requested.

If it is felt for any reason that direct communication with Applicant's attorney would serve to advance prosecution of this case to finality, the Examiner is invited to call the undersigned attorney at the below listed telephone number.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 16-2230.

Respectfully submitted,

Dated: June __, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims

Please amend claims 43, 62, 65, 66, 71, and 72 as follows:

43. A method for inactivating microorganisms and pyrogens present in biological materials comprising:

stabilizing a biological material on a solid carrier;

incubating said biological material in the presence of an alkyl phosphate-free detergent solution, said detergent solution containing at least one eluotropic salt in a total concentration of at least 200 mM; and

eluting said biological material from said detergent solution.

62. A method for inactivating microorganisms and pyrogens present in biological materials comprising:

stabilizing a biological material on a solid carrier;

incubating said biological material in the presence of an alkyl phosphate-free detergent solution, said detergent solution containing at least one eluotropic salt in a total concentration of at least 200 mM;

eluting said biological material from said detergent solution; and

purifying said biological material eluted from said detergent solution.

65. A method for inactivating microorganisms and pyrogens present in an activated prothrombin complex comprising:

reacting a mixture containing said activated prothrombin complex with a solid carrier such that said activated prothrombin complex is adsorbed on said solid carrier;

washing said solid carrier having said activated prothrombin complex adsorbed thereon;

incubating said solid carrier having said activated prothrombin complex adsorbed thereon in the presence of a tri-n-butyl phosphate (TNBP)-free TWEEN®-80 detergent solution, said detergent solution containing 30 mg/mL of sodium chloride;

eluting [said] a purified biological material from said tri-n-butyl phosphate (TNBP)-free TWEEN®-80 solution.

66. The method according to claim 65 wherein said mixture is [cryopercipitated] cryoprecipitated fresh human plasma.

71. The method according to claim 65 wherein said eluting is performed using a heparin solution such that a purified suspension of activated prothrombin complex is obtained.[.]

72. The method according to claim [72] 71 further comprising lyophilizing said purified suspension of activated prothrombin complex.